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REVIEW ARTICLE

Optic Nerve Sheath Diameter Sonography for the Diagnosis of Increased Intracranial Pressure in Nontraumatic Neurocritically Ill Patients: a Diagnostic Accuracy Systematic Review and Meta-Analysis

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Abstract

Background: Optic nerve sheath diameter (ONSD) assessed by ultrasound is a feasible bedside method for increased intracranial pressure (IICP) diagnosis. However, most of the evidence relies on the population of patients with traumatic brain injury, with few data available on other populations. Consequently, its efficacy in nontraumatic critically ill patients remains underexplored. Our purpose was to examine the accuracy of ONSD ultrasonography for diagnosing IICP in nontraumatic neurocritically ill patients.

Methods: We conducted a systematic search of PubMed, Embase, and the Cochrane Library databases for comparative studies of adult nontraumatic critically ill patients that evaluated the accuracy of sonographic ONSD for IICP diagnosis compared with invasive or noninvasive reference standards. Two reviewers independently completed the search, data abstraction, and quality assessment with Quality Assessment of Diagnostic Accuracy Studies-2 tool. Heterogeneity was examined with I^2 statistics. We used a bivariate model of random effects to summarize pooled diagnostic odds ratio, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and summary receiver operating characteristic.

Results: We included 18 observational studies, comprising 1,484 patients. Etiology of IICP was mixed, being composed of central nervous system infection, intracranial hemorrhage, acute ischemic stroke, aneurysmal subarachnoid hemorrhage, idiopathic intracranial hypertension, and hypoxic-ischemic brain injury. The pooled diagnostic odds ratio was 44.7 (95% confidence interval [CI] 22.5–80.1). Pooled sensitivity and specificity were 0.92 (95% CI 0.85–0.95) and 0.90 (95% CI 0.84–0.94), respectively, with a positive likelihood ratio of 6.19 (95% CI 4.4–8.5), and a negative likelihood ratio of 0.148 (95% CI 0.09–0.22). Summary receiver operating characteristic showed a calculated area under the curve of 0.925 (95% CI 0.84–0.927). Subgroup analysis of invasive and noninvasive reference standards showed similar accuracy of ultrasound ONSD for IICP diagnosis.

Conclusions: Ultrasound ONSD may be a potentially useful noninvansive tool for IICP diagnosis in patients with nontraumatic brain injury.

Keywords: Optic nerve sheath, Point-of-care ultrasound, Intracranial hypertension

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Introduction

Estimation of intracranial pressure (ICP) is a critical component of several neurological disorders, including, traumatic brain injury (TBI), aneurysmal subarachnoid hemorrhage (aSAH), intracranial hemorrhage (ICH), and acute ischemic stroke (AIS). Increased ICP (IICP) can lead to brain herniation, impaired cerebral perfusion, and subsequent brain damage or death [1–3]. Therefore, monitoring ICP allows for timely interventions to prevent poor outcomes [4].

Although invasive techniques, such as the use of intraventricular catheters (IVC) or intraparenchymal probe (IPP), are deemed the gold standard for their precision and for the IVC's capability to alleviate pressure by draining cerebrospinal fluid, they are associated with potential risks, including infections and hemorrhagic complications [5–7]. Invasive ICP assessment requires specialized multidisciplinary teams and is costly, being restricted to reference centers.

Radiological assessment, such as computed tomography (CT) and magnetic resonance (MRI), can also help for estimate the risk of IICP. However, these modalities are not widely available in all settings.

Among noninvasive tools for estimating ICP, optic nerve sheath diameter (ONSD) evaluated by ultrasound has gained interest because of its potential advantages of being feasible, repeatable, safe, low cost, and can be performed at the bedside [8]. The reliability of this method for diagnosing IICP has been evaluated in multiple systematic reviews and meta-analyses [9–12], mostly in the TBI population. However, its accuracy for evaluating IICP in nontraumatic neurocritically ill patients is not well known.

Therefore, we conducted a systematic review and meta-analysis of diagnostic test studies to evaluate the accuracy of sonographic ONSD among nontraumatic neurocritically ill patients.

Methods

This systematic review and meta-analysis was performed and reported in accordance with the Cochrane Collaboration Handbook for Systematic Review of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guidelines [13, 14]. As such, our protocol was registered on PROSPERO (ID: CRD42024596745).

Search Strategy

A systematic literature search was performed in the following databases: PubMed, MEDLINE/Embase, and the Cochrane Library. The search strategy developed combined terms such as intracranial hypertension, ultrasonographic ONSD and neurocritical-related terms. The detailed string is available in the Supplementary Material. Additionally, a backward search (snowballing) and a forward search (citation-tracking) were conducted for the included articles and relevant literature reviews. If the required data were not available in the published studies, we contacted the corresponding authors to obtain the information.

Study Screening and Selection

Two authors (RHM and LGP) independently screened titles and abstracts and then the full text of selected articles to identify eligible studies. Any disagreements were resolved through discussion with a third author (FSM).

We selected all English language articles assessing the ultrasonographic ONSD cutoff and its accuracy to diagnose IICP. The study population included patients aged ≥ 18 years with suspected IICP according to physical examination or imaging results, excluding the TBI population of any type. Suspected IICP was defined by any of the following physical examination findings: headache with alarming signals, vomiting, seizures, altered sensorium, or neurological deficit. All reference standards for diagnosis of IICP were accepted, such as CT, MRI, IPP, IVC, lumbar puncture, or external ventricular drainage. IICP by invasive methods was defined as ICP > 20 mm Hg for IVC/IPP or opening pressure on lumbar puncture > 20 cmH_2O. All study designs were included, except for case reports, preclinical studies, conference abstracts and case series. Moreover, included studies were required to have a 2 × 2 table of true positive, false negative, true negative, and false positive counts, either extracted from the original article or calculated from other reported information.

Data Extraction

Each included study was scrutinized independently by two authors to abstract the following data: study design, sample size, ultrassonography technique (probe, measurement procedure), year, country, median population age, female proportion, prevalence of IICP, diagnoses, reference standard for ICP measurement, sensitivity and specificity of ONSD for the diagnosis of IICP, and its cutoff value.

Quality Assessment

Two authors (RHM and LGP) independently performed the Quality Assessment of Diagnostic Accuracy Studies-2 tool [15] to evaluate risk of bias, tailored to suit the review question. Signaling questions were used to assess

the following domains: patient selection, index test, reference standard, and flow and timing. Risk of bias was assessed across each of the four domains and applicability across the first three domains. If a study had at least one high-risk domain, it was rated as having an overall high risk of bias. Disagreements about quality assessment were resolved by consensus with an additional author.

Statistical Analysis

We performed a meta-analysis of the studies using the reference standard of each study for IICP. Diagnostic effect measures were obtained from 2×2 contingency tables to calculate sensitivity,specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) with respective 95% confidence intervals (CIs). To account for heterogeneity in methodology and demographics across studies, a bivariate random-effects model was used, and forest plots were generated for graphical representation. We constructed summary receiver operating characteristic (SROC) models and calculated the area under the curve (AUC). In addition, we performed a subgroup analysis of the diagnostic accuracy of ultrasonography to determine pooled sensitivity and specificity associated with predefined covariate reference standard (invasive vs. noninvasive assessment of ICP).

We quantified heterogeneity of the included studies using the inconsistency index (I^2). Publication bias was assessed by analyzing funnel plot asymmetry and performing Egger's test. Statistical signifcance was assumed for $p < 0.05$. Statistical analysis was conducted using the R software/environment (version 4.4.0, R foundation for Statistical Computing).

Results

As shown in Fig. 1, the initial search yielded 2,574 results. After the removal of duplicate records and ineligible studies, 97 remained and were fully reviewed based on inclusion criteria. After further examination, 17 studies were included. One study was added after backward and forward research, resulting in 18 studies, comprising 1,484 patients.

Studies characteristics are displayed in Table 1. One study used a case–control design [16], another was

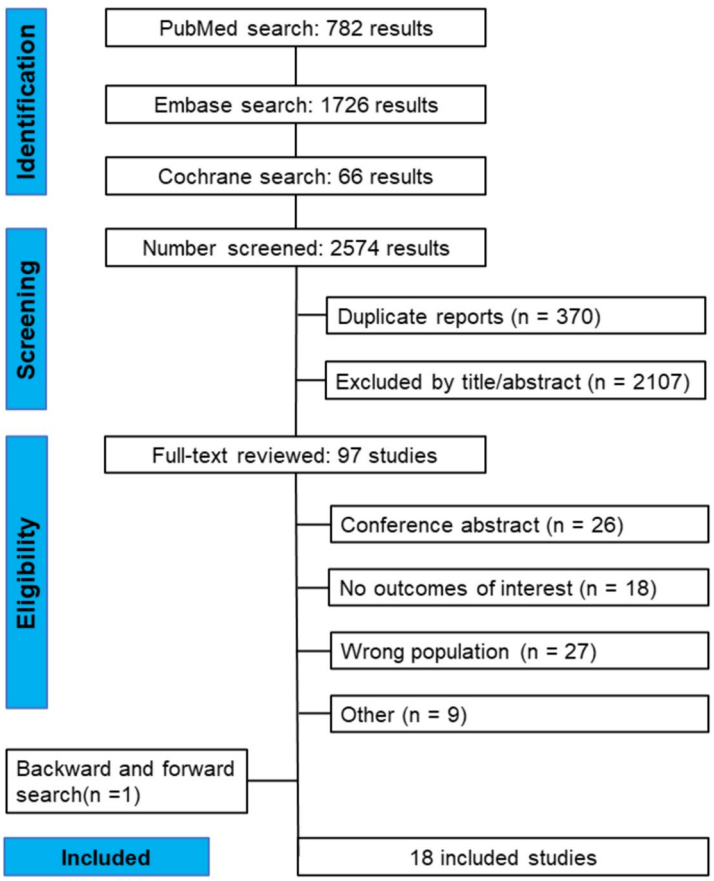

Fig. 1 PRISMA flow diagram of study screening and selection

Table 1 Baseline characteristics of included studies

Study	Population	Location	Design	Patients, *n*	Female, *n* (%)	Age, mean ± SD (yr)	IICP prevalence (%)	Transducer	ONSD cutoff (mm)	Reference standard
Batur 2023	AIS	Turkey	Case control	105	50 (47.6)	66.5 ± 14.3	35.2	Linear, 7.5 MHz	5.05	MRI
Bhide 2023	Mixed • 27.4% metabolic encephalopathies • 21.2% ICH • 20.4% AIS • 13.3% meningoencephalitis • 4.4% status epilepticus • 1.8% brain mass • 1.7% central venous thrombosis • 1.7% HIBI	India	Prospective cohort	114	46 (40.7)	64.05 ± 16.8	43	Linear, 7–15 MHz	5.7	CT/MRI
Bolesch 2015	IIH	Germany	Prospective cohort	36	N/A	N/A	42	Linear, 7–15 MHz	5.7	LP/EVD
Cardim 2019	HIBI	Canada	Prospective cohort	11	3 (27.3)	46.6	18	Linear, 7 MHz	5.95	IPP
Chopra 2022	Mixed • 57.5% brain mass • 27.5% tuberculous meningitis • 5% revision of shunt • 5% aqueductal stenosis • 2.5% supraclinoid aneurysm • 2.5% Neurocysticercosis	India	Prospective cohort	40	21 (52.5)	35.5	96.1	Linear, 6–13 MHz	5.85	IVC
Jeon 2017	Mixed • 61.2% ICH • 21% aSAH • 8.2% brain mass • 6.4% IVH • 3.2% hydrocephalus	South Korea	Prospective cohort	62	42 (67.7)	55.9 ± 14.3	51.6	Linear, 3 MHz	5.6	EVD
Kim 2024	aSAH	South Korea	Retrospective cohort	126	85 (67.46)	58.82 ± 14.86	53.1	Linear, 3.3–8 MHz	5.45	LP
Komut 2016	Mixed • 46% ICH • 34% AIS • 20% brain mass	Turkey	Prospective cohort	100	N/A	N/A	23	Linear, 11–14 MHz	5.3	CT
Lee 2016	Mixed • 86.4% ICH • 7.4% AIS • 6.2% brain mass	South Korea	Prospective cohort	134	53 (39.56)	63.86	75	Linear, 6–13 MHz	5.5	CT/MRI

Table 1 (continued)

Study	Population	Location	Design	Patients, *n*	Female, *n* (%)	Age, mean ± SD (yr)	IICP prevalence (%)	Transducer	ONSD cutoff (mm)	Reference standard
Lochner 2020	AIS	Germany	Prospective cohort	29	14 (48.27)	73.6	34.4	Linear, 3–11 MHz	5.6	CT
Moretti 2009	aSAH/ICH	Italy	Prospective cohort	63	N/A	N/A	30.8	Linear, 7.5 MHz	5.2	IPP/EVD
Naldi 2019	ICH	Italy	Prospective cohort	46	21 (45.65)	76.3	54.3	Linear, 7.5–11 MHz	5.6	CT
Oliveira 2022	AIS	Brazil	Prospective cohort	40	20 (50)	61 ± 19	45	Linear, 5–10 MHz	5.4	CT
Sahu 2021	Mixed • 73% brain mass • 13.3% aSAH • 10% aqueductal stenosis • 3.3% meningoencephalitis	India	Prospective cohort	30	17 (56.6)	32.73 ± 13.13	86.6	Linear, 6–13 MHz	5.5	IVC
Salahuddin 2016	Mixed • 47% metabolic encephalopathies • 21.5% seizures and meningoencephalitis • 17.6% AIS • 8.9% brain mass • 4.9% HIBI	Saudi Arabia	Prospective cohort	102	42 (41)	58 ± 20	30	Linear, 7.5–10 MHz	5.7	CT
Shirodkar 2014	Mixed • 60% meningoencephalitis • 34.2% AIS • 5.7% metabolic encephalopathies	India	Prospective cohort	60	17 (28.3)	56.15 ± 18.86	58.3	Linear, 10 MHz	4.71	CT/MRI
Wang 2015	Mixed • 55.9% meningoencephalitis • 15.4% AIS • 11.3% Non-CNS diagnosis • 9.3% seizures • 6% brain mass • 2.1% hydrocephalus	China	Cross-sectional	279	122 (43.7)	41.3 ± 15.1	36.2	Linear, 3–9 MHz	4.1	LP

Table 1 (continued)

Study	Population	Location	Design	Patients, *n*	Female, *n* (%)	Age, mean ± SD (yr)	IICP prevalence (%)	Transducer	ONSD cutoff (mm)	Reference standard
Yu 2023	Mixed • 72% meningoencephalitis • 12.1% central venous thrombosis • 9.3% AIS • 6.6% non-CNS diagnosis	China	Prospective cohort	107	45 (42.05)	44.96 ± 17.14	51.4	Linear, 5–14 MHz	4.68	LP

AIS acute ischemic stroke, *aSAH* aneurysmal subarachnoid hemorrhage, *CNS* central nervous system, *CT* computed tomography, *EVD* external ventricular drainage, *HIBI* hypoxic ischemic brain injury, *ICH* intracranial hemorrhage, *IIH* idiopathic intracranial hypertension, *IPP* invasive intraparenchymal probe, *IVC* intraventricular catheter, *IVC* intraventricular hemorrhage, *LP* lumbar puncture, *MRI* magnetic resonance, *N/A* not applicable, *ONSD* optic nerve sheath diameter, *SD* standard deviation

retrospective cohort [17], and one study had a cross-sectional design [18]; the remaining studies were prospective.The mean age varied from 35.5 to 76.3 years, and female prevalence ranged from 27.3% to 67.7%. The prevalence of IICP ranged from 18 to 96.1%.

Studies of mixed etiologies of brain injury accounted for 69.2% ($n=1,028$) of patients and etiology for raised ICP included cerebrospinal fluid disorders, meningitis, epilepsy, metabolic encephalopathies, brain tumor, and cerebrovascular accidents. The remaining studies involved ICH, AIS, aSAH, idiopathic intracranial hypertension and hypoxic-ischemic brain injury.

Nine studies comprising 730 patients used noninvasive methods as the reference standard for the diagnosis of IICP [15, 19–26]. CT was the most used noninvasive reference standard, followed by MRI. IICP was generally defined on imaging as significant brain edema, midline shift, compression of basal cisterns or ventricles, effacement of sulci, insufficient gray/white differentiation or brain herniation.

Ultrasonographic evaluation of ONSD was uniformly conducted using a linear ultrasound probe. However, the frequencies employed across different studies varied, with 7.5 MHz and 7 MHz emerging as the most commonly used frequencies. The methodology used for ONSD measurement in each study is detailed in the Supplementary Material.

Figure 2 depicts summary estimates of sensitivity and specificity for individual studies. The pooled DOR from the 18 studies for IICP diagnosis was 44.7 (95% CI 22.5–80.1).The pooled sensitivity and specificity were 0.92 (95% CI 0.85–0.95; $I^2=65\%$) and 0.90 (95% CI 0.84–0.94; $I^2=56\%$), respectively, with a PLR of 6.19 (95% CI 4.4–8.57) and a NLR of 0.148 (95% CI 0.09–0.22). The SROC curve had an AUC of 0.925 (95% CI 0.84–0.0.927), whereas the partial AUC was 0.78 (Fig. 3). The sensitivity and specificity stratified by reference standard of IICP diagnosis (invasive vs. noninvasive) showed similar estimates of accuracy of optic nerve ultrasonography (Fig. 4).

Sensitivity Analyses

In the leave-one-out sensitivity analyses, the overall pooled sensitivity remained stable across different iterations of the meta-analysis with individual studies omitted (Supplementary Fig. 3). The overall specificity revealed stable values across different iterations, but with a relevant decrease in heterogeneity ($I^2=41\%$) when one particular study was omitted [18].

Quality Assessment

Figure 5 displays the quality of all included studies evaluated using Quality Assessment of Diagnostic Accuracy

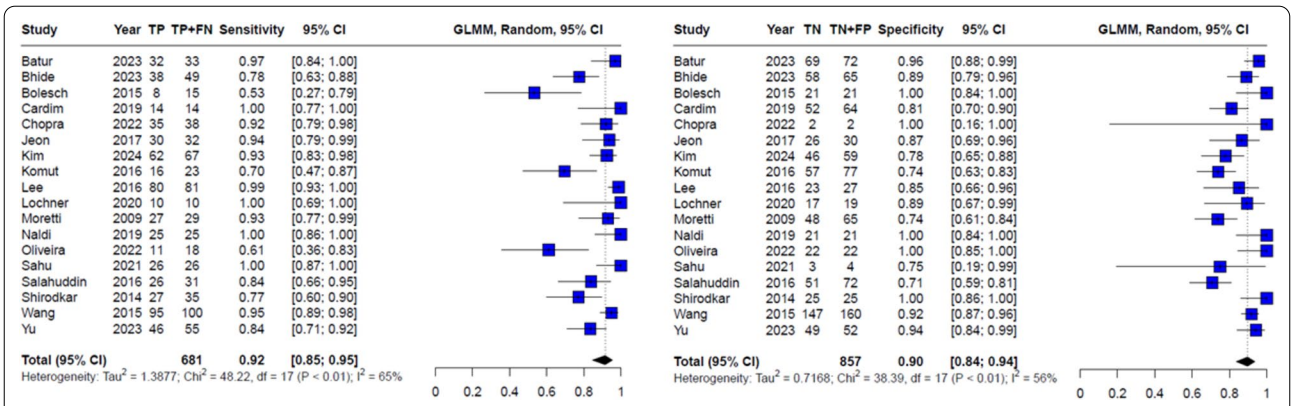

Fig. 2 Forest plot of pooled sensitivity (left) and specificity (right) of sonographic optic nerve sheath diameter for intracranial hypertension diagnosis. CI, confidence interval, FN, false negative, FP, false positve, GLMM, generalized linear midex models, TN, true negative, TP, true postive

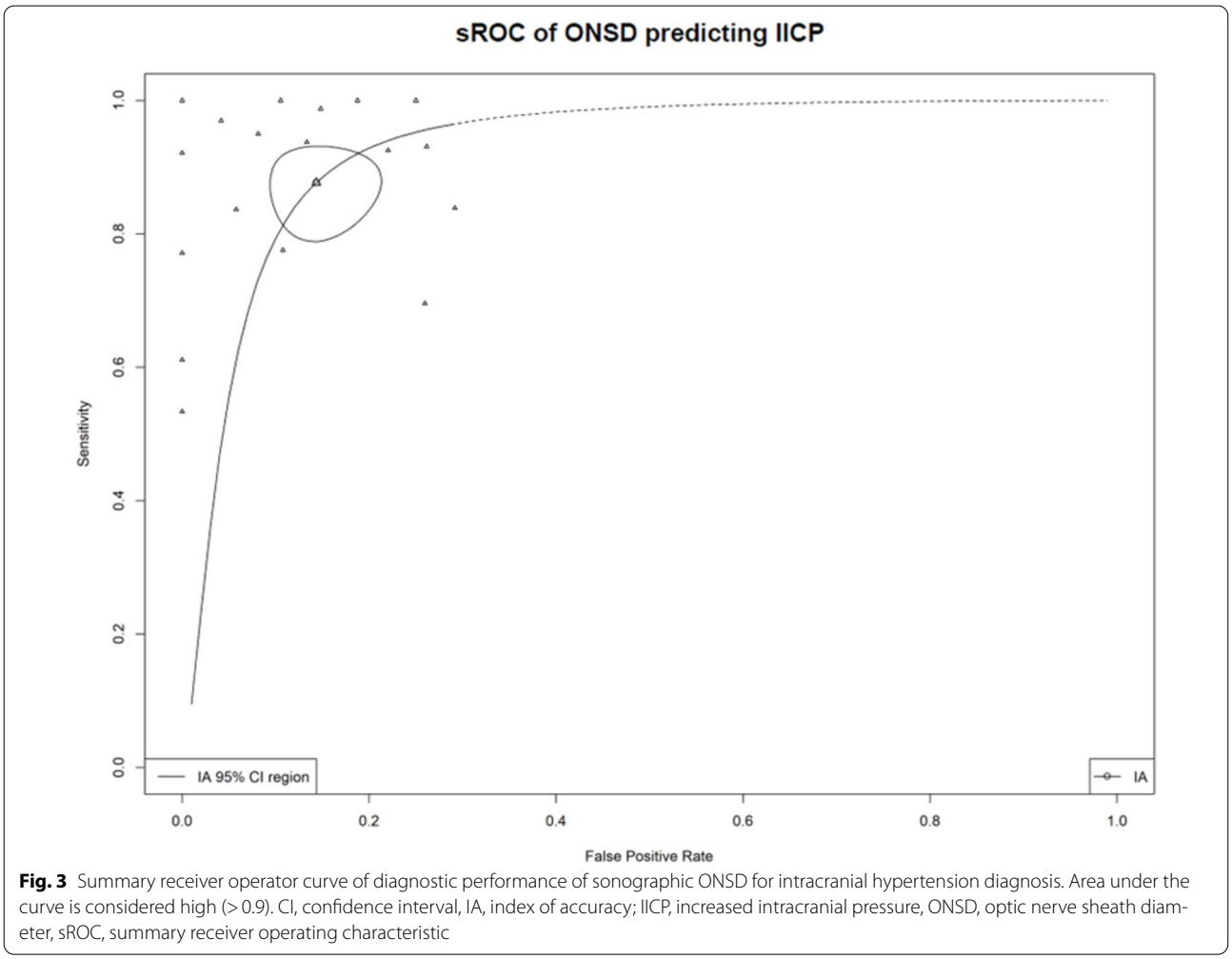

Fig. 3 Summary receiver operator curve of diagnostic performance of sonographic ONSD for intracranial hypertension diagnosis. Area under the curve is considered high (> 0.9). CI, confidence interval, IA, index of accuracy; IICP, increased intracranial pressure, ONSD, optic nerve sheath diameter, sROC, summary receiver operating characteristic

Studies-2 tool. Overall, the evaluation highlighted a generally low risk of bias, with some areas of concern within the assessed studies. Two studies presented an overall moderate risk of bias [17, 25]. A complete description of all four domains for each study is provided in the Supplementary Material.

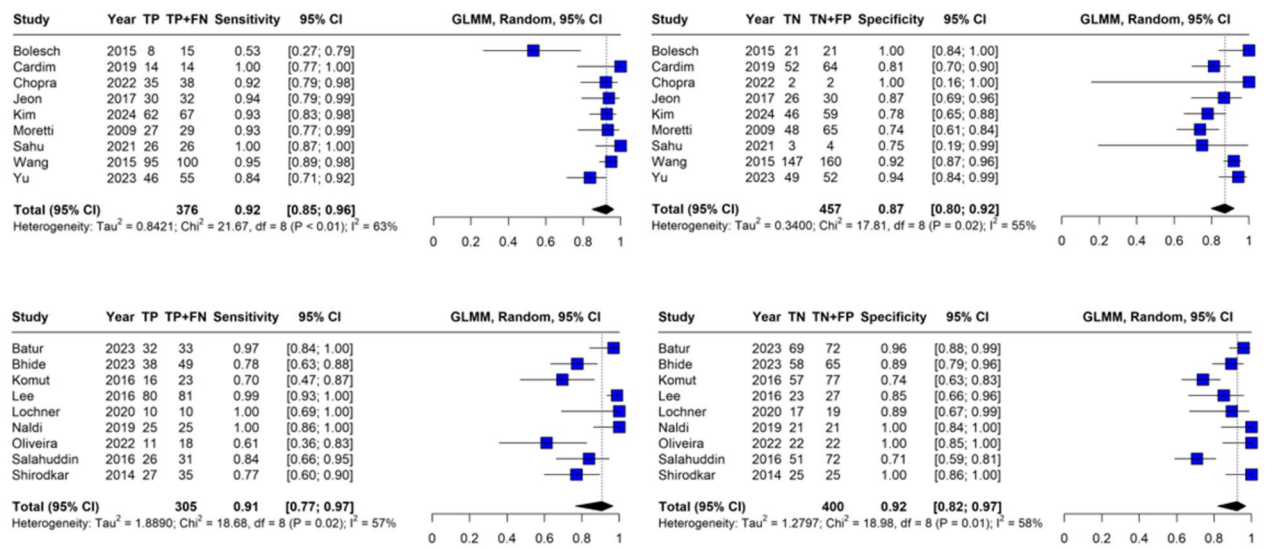

Fig. 4 Forest plot of pooled sensitivity and specificity of sonographic optic nerve sheath diameter for elevated intracranial pressure diagnosis, stratified by reference standard method: invasive (top) versus noninvasive (bottom). CI, confidence interval, FN, false negative, FP, false positve, GLMM, generalized linear mixed models, TN, true negative, TP, true postive

Funnel plot showed slight asymmetry on visual inspection (Fig. 6); however, Egger's regression test ($p=0.92$) did not find evidence of small study effect.

Discussion

In this meta-analysis encompassing 1,484 patients from 18 studies, we analyzed the accuracy of ultrasound ONSD in predicting IICP in nontraumatic neurocritically ill patients. We found a DOR of 44.7 and pooled sensitivity and specificity of 92% and 90%, respectively. Additionally, the AUC was 0.925, suggesting a high accuracy of ONSD ultrasound for diagnosing raised ICP. Accuracy estimates were similar for studies stratified by reference standards. To our knowledge, this is the most comprehensive meta-analysis showing the capacity of ultrasound ONSD in assessing ICP in nontraumatic neurocritically ill patients.

Raised ICP in nontraumatic brain injury can result from a variety of etiologies, each with distinct pathophysiological mechanisms. Overall, the exact prevalence of IICP due to nontraumatic causes is not uniformly reported across studies [27], but its occurrence is associated with increased morbidity and mortality regardless of etiology [28–31]. Current evidence advocates for treatment at an ICP threshold of 22 mm Hg in TBI guidelines, with cerebral perfusion pressure maintained between 60 and 70 mm Hg [31–34], but there are currently no specific guidelines available for ICP monitoring and management in the non-TBI population. Although invasive techniques are considered the gold standard, these may have several limitations as previously highlighted [5–7].

ONSD can be assessed using several techniques, including CT, MRI, and ultrasonography. Ophthalmic ultrasound, in particular, is noted for its significant diagnostic precision in identifying IICP. This method provides high sensitivity, effectively excluding elevated ICP in low-risk individuals, and has also demonstrated high specificity in confirming IICP among high-risk groups [9–12]. Besides its advantage of being a noninvasive, bedside, low-cost tool, it has shown to have a quite good reproducibility [35, 36], and it is reliable when compared with advanced imaging methods such as MRI [37]. However, significant variability has been observed in the methodology for ONSD image acquisition, and recent consensus on methodological issues related to ONSD has tried to standardize the technique to avoid heterogeneity [38].

Despite its numerous benefits, point-of-care ultrasound ONSD has several drawbacks. In patients with aSAH and stroke, evaluation of brain autoregulation is of critical importance; therefore, invasive and continuous measurement of ICP is needed [39–41], which is not possible with ultrasound ONSD assessment. Moreover, a variety of pathologies with differing mechanisms can lead to IICP. As a result, establishing a consistent ONSD cutoff to predict neurological outcomes and intracranial hypertension across different patient populations remains difficult.

Fig. 5 Quality assessment of included studies. Two studies presented some concerns (details of concerns in the Supplementary Material)

Our study has several limitations. First, we included mixed nontraumatic neurocritical care populations. Although the overall analysis suggests that ONSD sonography is a valuable tool for detecting IICP, each condition (e.g., meningoencephalitis, AIS, brain mass, SAH, IVH) may influence ICP dynamics uniquely, thus affecting the diagnostic reliability of ONSD measurements and its correlation with ICP. Consequently, our results should be interpreted with caution when applied to individual clinical scenarios. Second, different ONSD cutoff values were

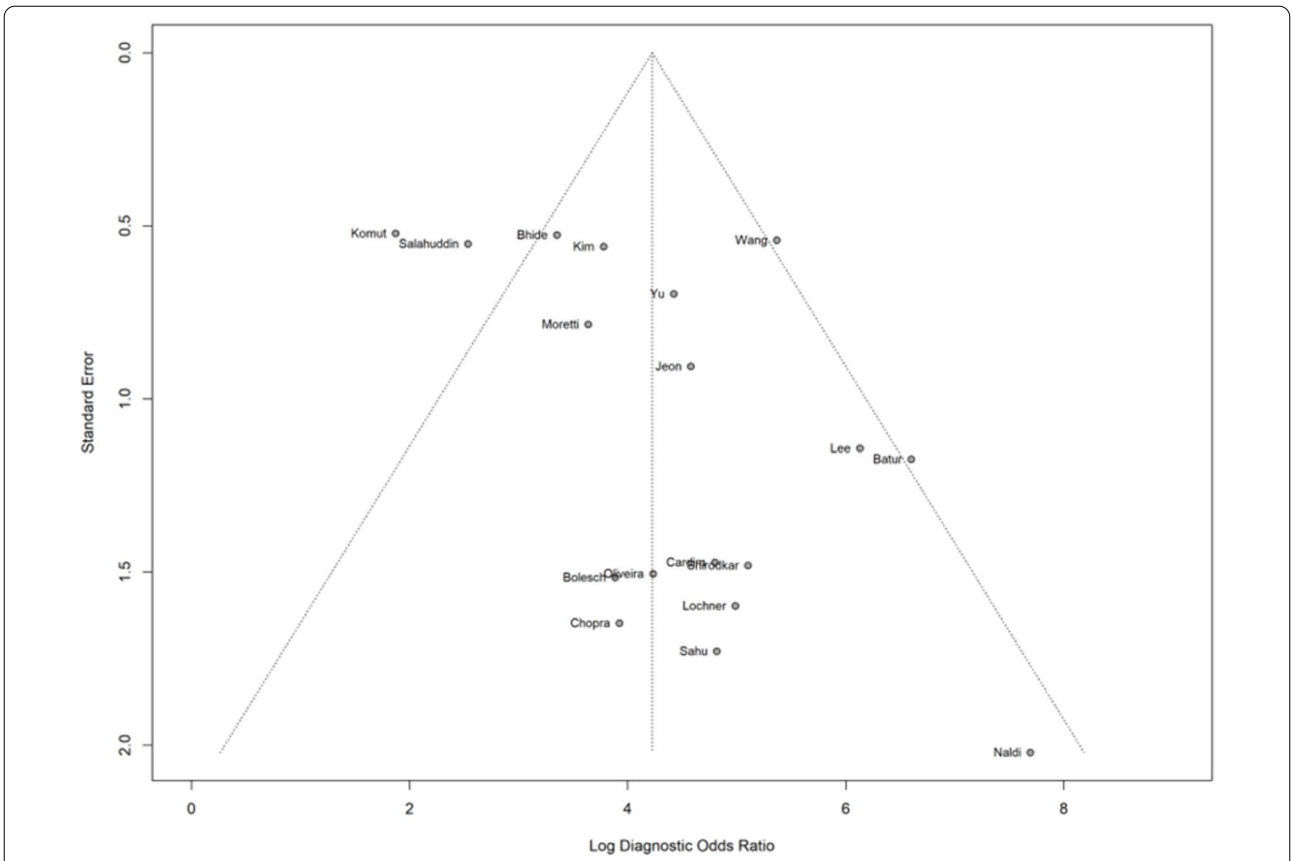

Fig. 6 Funnel plot asymmetry test for publication bias using Deek's model. Each point represents an individual study. The symmetrical distribution around the funnel's apex and a nonsignificant Egger's regression test ($p > 0.05$) suggest minimal publication bias

used across the studies.This reflects the heterogeneous patient populations and the lack of ONSD measurement standardization in real-world clinical practice. Third, the reference standard for IICP diagnosis was not homogeneous across studies, with most of them using an imaging method. Although this could impact the reliability of ultrasonography ONSD measurement, there were no relevant differences in diagnostic accuracy even in the subgroups analyses. Fourth, the leave-one-out sensitivity analysis revealed a significant decrease in heterogeneity in the specificity plot when the study by Wang et al. [18] was omitted. This particular study used a lower ONSD cutoff point of 4.1 mm for detecting IICP, which contrasts with the higher thresholds typically reported in Western cohorts. The distinct ethnic composition of the study population may introduce baseline physiological variations that could affect ONSD measurements. Moreover, being a cross-sectional study, it is susceptible to potential selection and confounding biases, which could further skew the results. Additionally, our meta-analysis revealed high heterogeneity in both pooled sensitivity and specificity across included studies. This heterogeneity may reflect variations in study populations, diagnostic thresholds, different reference standards, and operational definitions among studies. Although high sensitivity was consistently reported, the variability in specificity suggests that the diagnostic criteria and patient selection may substantially influence the accuracy. Some studies reported 100% specificity, which skewed the analysis and impacted the SROC results. Furthermore, the lack of etiology-specific stratification in studies of mixed populations, combined with an insufficient number of studies focusing on specific subgroups such as SAH, ICH, and AIS, precluded the conduct of meta-regression and subgroup analyses for these specific populations. These limitations may affect the generalizability of our findings across different neurological conditions. Despite these limitations, our results highlight the higher predictive value of ultrasound ONSD in patients with IICP. Such findings underscore the need for caution in generalizing the results without considering individual population contexts. Future research should aim to standardize

diagnostic criteria and methods to reduce variability and enhance comparability across studies.

Conclusions

Our findings suggest that sonographic measurement of ONSD holds potential as a noninvasive technique for assessing elevated ICP in patients with nontraumatic brain injury. However, because of the heterogeneity of the conditions in the mixed patient poupulations studied, these results should not be extrapolated uncritically to specific etiologies. This underscores the need for large-scale studies in diverse, non-TBI populations to better define the role of ultrasound ONSD in diagnosing intracranial hypertension and its integration into clinical workflows.

Supplementary Information

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Author Contributions

The authorship of this manuscript meets the criteria set forth by your journal. Each author has made a significant contribution to the research and writing of this document. Furthermore, all listed authors have reviewed and approved the final version of the manuscript and have agreed to its submission. Rafael Hortêncio Melo, MD: Conceptualization, data curation, methodology, writing—original draft preparation, review and editing, supervision. Luciana Gioli-Pereira, MD., PhD.: Data curation, formal analysis, investigation, writing—review and editing. Fábio Santana Machado, MD., PhD.: Writing, review and editing. Chiara Robba, MD., PhD.: Supervision, project administration, writing—review and editing.

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All authors report that no funding was received for this study.

Conflicts of interest

All authors report no relationships that could be construed as a conflict of interest. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Ethical Approval/Informed Consent

This meta-analysis involved secondary data from published studies, exempting it from Institutional Review Boad approval. Our protocol was registered with PROSPERO (ID CRD42024596745). We adhered to the Declaration of Helsinki's principle that "the well-being of the individual research participant must take precedence over all other interests."

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